UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,758	05/25/2005	Andreas Bergmann	2582.016	4935

23405 7590 03/21/2007

HESLIN ROTHENBERG FARLEY & MESITI PC
5 COLUMBIA CIRCLE
ALBANY, NY 12203

EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,758	BERGMANN ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *4,14-16 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-13 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *25 May 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 18) in the reply filed on 21 December 2006 is acknowledged. Furthermore, Applicants elected several species in relation to Group I, first, immunodiagnostic assay, which reads on claims 1-13, 16 and 17; second, precalcitonin for use in sepsis diagnosis, which reads on claims 1-17; third, SEQ ID NO: 13, which reads on claims 1-3 and 5-17.

Claims 4, 14-15 and 18 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species and invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 21 December 2006. Claims 1-3, 5-13 and 16-17 are under examination insomuch as they read on the elected species. Note also that claims 16 and 17 are only examined insomuch as they read on the elected species SEQ ID NO: 13, not SEQ ID NO: 16 (LAP-1).

Claim Objections

Claims 1-3, 5-13 and 16-17 are objected to because of the following informalities: for the sake of clarity, LASP-1 and LAP-1 should be spelled out in the independent claims and/or first use followed by LASP-1 and LAP-1 in parentheses. Appropriate correction is required.

Claims 13-16 are objected to because of the following informalities: the claims recite non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5-13 and 16-17 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites a method for the determination of the presence and/or amount of the protein LASP-1....for the purpose of medical diagnosis", however, "the purpose of medical diagnosis" is interpreted as an intended use phrase. Without a recitation of a method step, the intended use phrase does not breathe life and meaning into the claim. Note that claims 2-3 contain the recitation "and conclusions are drawn with respect to the presence, the expected course...", thus constitute a complete recitation of a method with no omission. For the purposes of prior art, claim 1 encompasses measuring LASP-1 for any purpose.

Claims 5-13 and 16-17 are rejected because they depend (either directly or indirectly) from an indefinite claim.

Claims 1-3, 5-13, 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite (or depend from claims that

recite, "at least substantially identical in sequence." This phrase is indefinite. See MPEP 2173.05, Relative Terminology. "At least substantially" is similar to "at least about", which was held to be indefinite. The claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant (see MPEP 2171).

Claims 2, 3, 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "in particular, sepsis-like" following " inflammatory diseases and infections" (claims 2-3), or "in particular Alzheimer's disease" following "inflammatory diseases of the brain" (claim 10) or "in particular cardiac infarction" following "cardiac disease" (claim 11). A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74

(Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance claims 2, 3, 10 and 11 recites the broad recitation "inflammatory diseases..." (claims 2, 3, 10) or "cardiac disease" (claim 11), and the claim also recites sepsis like (claims 2, 3), Alzheimer's disease (claim 10) or "cardiac disease" (claim 11), which is the narrower statement of the range/limitation.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 13 recites the

broad recitation "soluble cytokeratin fragments", directly followed by "in particular CYFRA 21...", which is the narrower statement of the range/limitation.

Claims 2-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "sepsis-like", and it is unclear whether Applicants mean to claim sepsis only or conditions related to sepsis but that are not clinically categorized as sepsis. The claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant (see MPEP 2171).

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what is meant by the term "a liquor" and what Applicants intend to be covered by this term. The claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant (see MPEP 2171).

Claim 16 recites the limitation "method according to claim 1...a determination of LASP-1 and LAP-1 is carried out". There is insufficient antecedent basis for this limitation in the claim because claim 1 makes no mention of LAP-1.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3, 5-13 and 16-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The claims are drawn to medical diagnosis, early medical diagnosis, prognosis and assessment of the severity or therapy-accompanying monitoring of a host of conditions including inflammatory conditions and infections, sepsis, Alzheimer's disease, cardiac infarction, diseases of the central nervous system, cancer. Inflammation is defined very generally at p. 3-4 of the specification as

> [Certain] physiological reactions of an organism to different types of external effects, such as, for example injuries, burns, allergens, infections by microorganisms, such as bacteria and fungi and viruses to foreign tissues which trigger rejection reactions or to certain endogenous states of the body which trigger inflammation, for example, in autoimmune diseases and cancer. Inflammations [sic] may occur as harmless, localized reactions of the body but are also typical features of numerous serious chronic and acute diseases of individual tissues, organs, organ parts and tissue parts.

If LASP-1 protein levels changed (i.e., in the case of what is disclosed in the instant specification, protein levels are up-regulated) with every type of medical condition, infection or inflammatory condition described in the specification, the person of skill in the art would have difficulty using such an assay for diagnosis because a biomarker that is up-regulated for any type of medical condition would not be specific, thus would not be an effective biomarker for a particular type of disease. A biomarker is defined as "cellular, biochemical, or molecular alterations that are measurable in biological media

such as human tissues cells or fluids or in the case of exposures, can be any parameter that is used to measure an interaction between a biological system and an environmental agent. Implicit in this definition is the need for a biomarker to have a certain degree of specificity for a particular disease (see Richard Mayeux, NeuroRx. 2004; 1: 182-188, whole document and p. 182, 1st paragraph). Mayeux addresses this at p. 186, left column, 2nd paragraph:

> The evaluation of the validity of a biomarker is complex...three aspects of measurement validity: 1) content validity, which shows the degree to which a biomarker reflects the biological phenomenon studied, 2) construct validity, which pertains to other relevant characteristics of the disease or trait, for example other biomarkers or disease manifestations, and 3) criterion validity, which shows the extent to which the biomarker correlates with the specific disease and is usually measured by sensitivity, specificity, and predictive power.

With regard to the first and third criteria, if LASP-1 changes (i.e. is up-regulated) in response to almost any manifestation of disease or inflammation, than measuring LASP-1 up-regulation in a sample would not correlate to any specific disease but only a general malaise. Alternatively, since the specification discloses that LASP-1 levels are found only at very low levels in healthy individuals (see p. 11, lines 11-24, for instance), such a test could be indicative of the absence of disease, however, this would not be informative with regard to diagnosis, prognosis and assessment of the severity or therapy-accompanying monitoring.

Claim 1 indicates that the purpose of the claimed invention is for medical diagnosis. Mayeux addresses the use of biomarkers in medical diagnosis at p. 186, left column, 3rd paragraph:

> Most would agree that screening tests would be very desirable for chronic progressive disorders. One purpose of screening is early detection with the hope of preventing the

illness altogether. Many of the methods and concerns related to diagnostic testing apply to screening as well. As with other diagnostic methods, sensitivity and specificity tell us the accuracy of the test but not the probability of disease. For that we need to estimate the predictive values (positive and negative). Positive predictive value (PPV) is the percentage of people with a positive test who actually have the disease. This provides us with information about the likelihood of the disease being present if the test is positive. Negative predictive value (NPV) is the percentage of people with a negative test who do not have the disease. Increasing the prior probability will increase the PPV but decrease the NPV, assuming that the sensitivity and specificity remain unchanged. Similar changes in the predictive values occur with changes in the prevalence of a condition as will be discussed in screening.

In other words, in order to be useful as a diagnostic assay, the test must predict accurately the number of people who do (or do not) have a particular disease. In the instant case, Applicants' provide compelling evidence for the upregulation of LASP-1 in three unrelated conditions: sepsis, Alzheimer's disease and cardiac infarction, at p. 24 and Figures 4; 5 and 6 of the specification, but not only are the LASP-1 levels all upregulated in the sera of patients with these three unrelated conditions, the relative levels of LASP-1 in the ill individuals is similar. It is not clear how the test can differentiate between these different conditions. Furthermore, with respect to the relative levels of LASP-1 being similar in ill individuals, it is not clear how the person of ordinary skill in the art could use that information to draw conclusions "with respect to the presence, the expected course, the severity or the success of a therapy of the inflammatory disease or of the infection from the presence and/or amount of the LASP-1 immunoreactivity determined" as recited in claims 2, 3, for example. One of ordinary skill in the art could not draw conclusions about the course, severity or success of therapy in inflammatory diseases without a specific biomarker for a particular disease and without any difference in LASP-1 levels between disease types. Nor could one of

ordinary skill in the art use the claimed assays for prognosis and assessment of the severity or therapy-accompanying monitoring if the results of the test (as indicated in the specification) merely show either the presence (in ill individuals) or absence (in healthy individuals) of LASP-1 protein. As stated above, ill individuals appear to have similar general levels of LASP-1, and no information is provided in the specification as to how to differentiate between an individual at the early part of the disease, nor how levels of LASP-1 can be correlated to disease severity (prognosis) or therapy assessment. Finally, in the instant case, the silence of the literature on the utility of measuring LASP-1 in biological fluids of patients for the purpose of medical diagnosis, prognosis and therapy assessment contributes to the unpredictability of the art, and the lack of support for a specific utility of the claimed assays, which is discussed further below under Rejections under 35 U.S.C. 112, first paragraph –Enablement.

Claim Rejections - 35 USC § 112, first paragraph – Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-13 and 16-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, there are other issues to be considered under 35 U.S.C. 112, first paragraph for enablement in the instant claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claims are broad and recite determination of the presence or absence of LASP-1 protein or of a protein which is at least substantially identical in sequence to it, at least in the range of the first 200 amino acids, or of an immunoreactive fragment of such a protein, in free and/or protein-bound form or posttranslationally modified form in a biological fluid of a patient. Certain positions in the sequence of a protein are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. The specification (and claim 5) indicates at p 23, lines 28-33 to p. 24, lines 1-3 that immunoreactivity of LASP-1 occurred amino acid residues 121-137, 147-159 and 170-187 of LASP-1. , however, immunoractive

encompasses any fragment, because it is not the same as "antigenic". Critical regions of antigenicity can tolerate only relatively conservative substitutions or no substitutions, however, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if critical regions are identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity, and the claims encompasses mutation of non-essential residues as well as essential residues. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

As discussed above under Rejections under U.S.C. 101, the scope of claim 1 (medical diagnosis) and claims reciting "inflammatory disease" or "infection" or "diseases of the central nervous system" are broad and encompasses a great many unrelated diseases and conditions. Furthermore, biological fluid is broad and encompasses tears, sweat, urine and semen, to name a few, and there is no guidance

in the specification or the literature that all body fluids could be used in the claimed assays. The breadth of the claims is not supported in the literature or the specification. The person of skill in the art would have to undertake an unreasonable amount of experimentation to determine which of the diseases encompassed by the claims could be diagnosed by an immunoassay measuring LASP-1 protein in a biological fluid and to be able to draw conclusions about and conclusions "with respect to the presence, the expected course, the severity or the success of a therapy of the inflammatory disease or of the infection from the presence and/or amount of the LASP-1 immunoreactivity determined", as recited in claims 2-3, for example. The reasons for this is discussed in greater detail above in the Rejections under U.S.C. 101, and the issues raised there are applicable here. The state of the prior art is such that there is little guidance with respect to medical diagnosis, prognosis and therapy assessment comprising measuring LASP-1 in an immunoassay, thus illustrating that there is a high level of unpredictability in this field. Although Applicants provide compelling evidence for the up-regulation of LASP-1 protein in patients with sepsis, Alzheimer's disease and cardiac infarction at p. 24 and Figures 4, 5 and 6 of the specification, there is no support in the specification or the literature for diagnosis as broadly stated in claims 1-3 or for diagnosis of inflammatory disease or infection in general. Inflammation is defined very generally at p. 3-4 of the specification as

> [Certain] physiological reactions of an organism to different types of external effects, such as, for example injuries, burns, allergens, infections by microorganisms, such as bacteria and fungi and viruses to foreign tissues which trigger rejection reactions or to certain endogenous states of the body which trigger inflammation, for example, in autoimmune diseases and cancer. Inflammations [sic] may occur as harmless,

localized reactions of the body but are also typical features of numerous serious chronic and acute diseases of individual tissues, organs, organ parts and tissue parts.

Furthermore, if LASP-1 protein levels changed (i.e., in the case of what is disclosed in the instant specification, protein levels are up-regulated) with every type of medical condition, infection or inflammatory condition described in the specification, the person of skill in the art would have difficulty using such an assay for diagnosis because a biomarker that is up-regulated for any type of medical condition would not be specific, thus would not be an effective biomarker (discussed in greater detail above under Rejections under 35 U.S.C. 101).

Due to the large quantity of experimentation necessary for which diseases the claimed methods would be effective and to determine the levels of LASP-1 that correlate to particular disease states for the purpose of diagnosis, prognosis and assessment of therapy, the lack of direction/guidance presented in the specification regarding and the absence of working examples directed to the same, the complex nature of the invention, the unpredictability of the effects of mutation on protein structure and function (see discussion above and recited references with regard to the broad recitation of LASP-1), and the breadth of the claims which fail to recite limitations on disease states for which the claimed methods can be used, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6, 7, 11, 12 and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Rio et al. (U.S. Patent 5,981,218, issued 9 November 1999). The claims recite a method for the determination of the presence and/or amount of the protein LASP-1 (SEQ ID NO: 1) or of a protein which is at least substantially identical in sequence to it, at least in the range of the first 200 amino acids, or of an immunoreactive fragment of such a protein, in free and/or protein-bound form or posttranslationally modified form in a biological fluid of a patient for purposes of medical diagnosis (1, 16, 17), wherein the method is carried out for early diagnosis and diagnosis, for prognosis and assessment of the severity and therapy-accompanying monitoring of inflammatory diseases and infections, in particular sepsis-like systemic infections, and conclusions are drawn with respect to the presence, the expected course, the severity or the success of a therapy of the inflammatory disease or of the infection from the presence and/or amount of the LASP-1 immunoreactivity determined (2); characterized in that the immunoreactivity of a posttranslationally formed soluble form of LASP-1 and/or LAP-1 is determined (6); characterized in that the biological fluid is blood, a blood fraction or liquor (7); a method for early diagnosis and diagnosis, for prognosis and assessment of the severity and for therapy-accompanying monitoring of

inflammatory diseases and infections, in particular sepsis-like systemic infections, characterized in that the presence and/or amount of the protein LASP-1 (SEQ ID NO: 1) or of a protein which is at least substantially identical in sequence with it, at least in the range of the first 200 amino acids, or of an immunoreactive fragment of such a protein, in free and/or protein-bound form in a tissue sample of a patient are determined, and conclusions are drawn with respect to the presence, the expected course, the severity or the success of a therapy of the inflammatory disease or of the infection from the presence and/or amount of the proteins determined (3); wherein the disease is cardiac disease, cardiac infarction, a disease of the central nervous system or cancer (11), and wherein the assay is carried out as part of a multi-parameter determination in which at last one further disease-relevant parameter is simultaneously determined and in which a measured result in the form of a set of at least how measured quantities is obtained and is evaluated for the fine diagnosis of the inflammation or infection (12).

The '218 patent teaches a prognostic immunoassay (radioimmunoassay) in which the LASP-1 polypeptide is used for prognosis of breast cancer and in which the prognostic assay is carried out in cytosol (see column 25, lines 16-40), thus encompassing claims 1-3, 6, 7, 11 and 16-17. Note that claim 1 is indefinite for omitting a step, thus is interpreted as measurement of LASP-1 for any reasons, including prognosis. In addition, note that breast cancer is interpreted as an inflammatory condition or infection because the specification defines inflammation as resulting from cancer at p. 4, lines 1-6). Note also that since claim 16 was only examined insomuch

as it read on the elected species, it is interpreted as measurement of LASP-1 only (LAP-1, i.e., SEQ ID NO: 16 was not elected). Furthermore, the '218 patent teaches that numerous polypeptides can be used in the prognosis of breast cancer (see columns 24 through 26, where several peptides are discussed in the context of being useful for breast cancer prognosis) thus meet the limitations of claim 12, because it flows from the specification of the '218 patent that the prognostic assays can be carried out simultaneously. Finally, the '218 contains the same sequence of LASP-1 as taught in the instant application:

```
RESULT 1
US-08-691-814B-4
; Sequence 4, Application US/08691814B
; Patent No. 5981218
;  GENERAL INFORMATION:
;    APPLICANT:  Rio, Marie-Christine
;    APPLICANT:  Tomasetto, Catherine
;    APPLICANT:  Basset, Paul
;    APPLICANT:  Byrne, Jennifer
;    TITLE OF INVENTION:  Isolated Nucleic Acid Molecules Useful
;    TITLE OF INVENTION:  as Leukemia Markers and in Breast Cancer Prognosis
;    NUMBER OF SEQUENCES:  124
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Sterne, Kessler, Goldstein & Fox P.L.L.C.
;      STREET:  1100 New York Ave, NW, Suite 600
;      CITY:  Washington
;      STATE:  DC
;      COUNTRY:  USA
;      ZIP:  20005-3934
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.30
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/691,814B
;      FILING DATE:  31-JUL-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 60/002,183
;      FILING DATE:  09-AUG-1995
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Steffe, Eric K.
;      REGISTRATION NUMBER:  36,688
```

```
;       REFERENCE/DOCKET NUMBER:  1383.0090001
;     TELECOMMUNICATION INFORMATION:
;       TELEPHONE:  202-371-2600
;       TELEFAX:  202-371-2543
;   INFORMATION FOR SEQ ID NO:  4:
;     SEQUENCE CHARACTERISTICS:
;       LENGTH:  261 amino acids
;       TYPE:  amino acid
;       TOPOLOGY:  linear
;     MOLECULE TYPE:  protein
US-08-691-814B-4

  Query Match             100.0%;  Score 1420;  DB 1;  Length 261;
  Best Local Similarity   100.0%;  Pred. No. 3.1e-137;
  Matches  261;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 MNPNCARCGKIVYPTEKVNCLDKFWHKACFHCETCKMTLNMKNYKGYEKKPYCNAHYPKQ 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MNPNCARCGKIVYPTEKVNCLDKFWHKACFHCETCKMTLNMKNYKGYEKKPYCNAHYPKQ 60

Qy         61 SFTMVADTPENLRLKQQSELQSQVRYKEEFEKNKGKGFSVVADTPELQRIKKTQDQISNI 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 SFTMVADTPENLRLKQQSELQSQVRYKEEFEKNKGKGFSVVADTPELQRIKKTQDQISNI 120

Qy        121 KYHEEFEKSRMGPSGGEGMEPERRDSQDGSSYRRPLEQQQPHHIPTSAPVYQQPQQQPVA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 KYHEEFEKSRMGPSGGEGMEPERRDSQDGSSYRRPLEQQQPHHIPTSAPVYQQPQQQPVA 180

Qy        181 QSYGGYKEPAAPVSIQRSAPGGGGKRYRAVYDYSAADEDEVSFQDGDTIVNVQQIDDGWM 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 QSYGGYKEPAAPVSIQRSAPGGGGKRYRAVYDYSAADEDEVSFQDGDTIVNVQQIDDGWM 240

Qy        241 YGTVERTGDTGMLPANYVEAI 261
              |||||||||||||||||||||
Db        241 YGTVERTGDTGMLPANYVEAI 261
```

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D. can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Christina Borgeest, Ph.D.

ELIZABETH KEMMERER
PRIMARY EXAMINER